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Board of Registration in Pharmacy

Advisory: HVAC Excursions

This document outlines the Board of Registration in Pharmacy's ("Board") recommendations regarding a pharmacy's response and remediation of Heating, Ventilation, and Air Conditioning ("HVAC") system excursions in sterile compounding environments (ISO-classified spaces and segregated compounding areas).

HVAC excursions addressed through this advisory include temperature, humidity, and differential pressure(s) resulting from inadequate HVAC system performance and planned or unplanned interruption of HVAC system operation that may impact the state of control of a sterile compounding environment.

Definitions:

Excursion means a value that is outside of acceptable ranges or specifications based on industry standards or regulatory requirements.

Excursion limit means the point in which an excursion reaches an alert or action level.

Alert level means an excursion limit value that when met or exceeded constitutes an early warning of a drift from normal operating conditions but does not necessarily require corrective action.

Action level means an excursion limit value that when met or exceeded requires an investigation and corrective action.

Normal operating range means the baseline values likely to be encountered by a facility under normal operating conditions.

Recovery time means a validated measurement of the elapsed time for primary and secondary engineering controls to be restored to acceptable ranges or specifications based on industry standards or regulatory requirements after an excursion.

I. General Recommendations

A. Define facility-specific excursion limits:

i. Establish normal/expected operating range or values for temperature, humidity, and differential pressure under dynamic operating conditions. Continuous monitoring devices or systems with alarm features are recommended for all sterile compounding environments.
ii. Establish alert and action levels for excursions (value and duration). Consider normal operating range (baseline), trending data, and excursion history. Facilities should work with a qualified vendor in establishing excursion alert and action levels.
iii. Develop appropriate response plans for excursion alert and action levels.
iv. Excursion limits should be reassessed on at least an annual basis and any time there is a renovation or change in configuration or square footage of the compounding area.

B. Develop written policies and procedures pertaining to:

i. monitoring and documentation requirements for temperature, humidity, and differential pressure
ii. response to alert levels
iii. response to action levels
iv. the manner in which HVAC excursions are investigated and responded to
v. response plan for interruption of HVAC system operation (planned or unplanned)
vi. response plan for power loss / outage
vii. conducting a risk assessment of product, environment, etc.

C. Engage a qualified HVAC engineer to:

i. develop an HVAC preventative maintenance plan to include routine assessment, calibration, and maintenance of measuring devices used for temperature, humidity, differential pressures, and particle count (as applicable)
ii. develop testing / maintenance plan for uninterrupted power sources (i.e., generator), if utilized

D. Engage a qualified certification vendor to determine the following in the event of an HVAC system malfunction or power loss:

i. Elapsed time to reach excursion limits (i.e., alert and action levels) in compounding areas
ii. Recovery times of each primary and secondary engineering control

NOTE: Ideally, these studies should be conducted prior to the commissioning of new compounding facilities. In the case of existing compounding facilities, it is recommended that these studies be conducted in conjunction with certification to minimize disruption to operations.

II. General Response Plan for All Excursions

A. Document / record the excursion (e.g., value, duration, time of day, etc.).

B. Visually inspect the sterile compounding environment for any obvious signs or factors that may be contributing to the excursion such as incorrect thermostat settings, open doors, ceiling breaches, or obstruction of HEPA filter or return vents.

C. For excursions reaching alert levels, monitor on a more frequent basis and continually assess the situation in accordance with the facility's policies and procedures.

D. For excursions reaching action levels:

   i. Conduct a risk assessment of any products (e.g., in-process, finished, etc.) that were subjected to the excursion and determine if these products are safe to dispense / utilize. The risk assessment should consider factors including the type of compounding conducted (i.e., contamination risk level), nature of the process, route of administration, volume (e.g., single unit, batch production, etc.), product storage conditions, and beyond use date ("BUD") assignment.

   ii. Consider limiting or suspending compounding until a remediation plan is developed and implemented. Conduct a risk assessment before choosing to compound during remediation.[1]

   iii. Conduct an investigation into possible causes. If necessary, contact a qualified HVAC engineer / professional to remediate.

   iv. Depending on the nature of the remediation activities, recertification of primary and secondary engineering controls may be required.

   v. Once the cause of the excursion has been remediated and the sterile compounding environment has recovered in accordance with the

[1] Pharmacies suspending sterile compounding activities must implement the pharmacy's continuity of care plan to ensure patients' needs are met during the remediation process.

validated recovery time, initiate cleaning procedures. Based on the nature and duration of the excursion, consult with a microbiologist, infection control professional, or industrial hygienist for guidance on cleaning procedures and conducting environmental monitoring ("EM").

vi. Unless using a continuous monitoring device with an alarm, monitor and document hourly or more frequently for at least one day to ensure the HVAC system is operating normally.

vii. After all remediation activities have been completed and the sterile compounding environment has fully recovered, a facility may consider resuming normal sterile compounding activities.

III. Response to Temperature and Humidity Excursions

Sterile compounding pharmacies with an excursion in temperature or relative humidity should follow the "General Response Plan for All Excursions" above.

For excursions at or above action levels, and after initiation of remediation activities, a pharmacy choosing to resume sterile compounding should limit BUDs as follows until remediated:

ISO-classified spaces:
no more than 24 hours room temperature or 72 hours refrigerated

Segregated compounding areas:
follow the requirements for "Immediate Use CSPs" as defined in the most current chapter of USP

Relevant Standards:
USP <797> (2021 revised draft):
The cleanroom suite should be maintained at a temperature of 20°C (68°F) or cooler and a relative humidity below 60% to minimize the risk for microbial proliferation and provide comfortable conditions for compounding personnel attired in the required garb. The temperature and humidity must be monitored in each room of the cleanroom suite each day that compounding is performed, either manually or by a continuous recording device.

USP <659>:
Controlled room temperature means the temperature that is maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F).

USP <1066>:
Preparation and Compounding: Humidity should be monitored and controlled, because drugs tend to degrade in the presence of moisture. Because of its effect on drug stability and integrity, the humidity in compounding and storage areas is second in importance only to temperature (see USP <795> and <797>).

IV. Response to Differential Pressure Excursions

Sterile compounding pharmacies with an excursion in differential pressure should follow the "General Response Plan for All Excursions" above.

During an excursion, a pharmacy may choose to engage in sterile compounding activities, depending on the ISO-classified area, in accordance with the following conditions until remediated:

A. ISO-5 Primary Engineering Control ("PEC")

ISO-5 PECs should be equipped with a pressure differential gauge or similar measuring device. If there is a differential pressure excursion exceeding the manufacturer's specifications, compounding in an ISO-5 PEC should be suspended.

If there are multiple PECs within the compounding area, the pharmacy may use the unaffected PEC(s) if the buffer room is able to maintain the required minimum air changes per hour without the affected PEC.

B. ISO-7 Negative Pressure (Hazardous Drug) Buffer Room

Suspend sterile compounding.

C. Other ISO Classified Spaces (ISO-7 Non-Hazardous Drug Buffer Room, ISO-7 Ante Room, ISO-8 Ante Room, or Other ISO-8 Classified Space)

Limit BUDs to no more than 12 hours.

NOTE: If an ISO-8 classified space does not immediately precede an ISO-7 non-hazardous buffer room (e.g., air lock, prep room, etc.), limit the BUDs to no more than 24 hours room temperature or 72 hours refrigerated.

Relevant Standards:

USP <797> (2021 revised draft):

In a cleanroom suite, a minimum differential positive pressure of 0.020-inch water column is required between each ISO-classified area (e.g., between the buffer room and ante-room). The pressure differential between the ante-room and the unclassified area must not be less than 0.020-inch water column. Where pressure differentials are required, a pressure differential monitoring device must be used to continuously monitor the pressure differentials.

USP <800>:

The C-PEC is placed in an ISO-7 buffer room that has fixed walls, HEPA-filtered supply air, a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas and a minimum of 30 ACPH.

V. Documentation Requirements

Document all actions and responses related to the HVAC excursion, including risk assessment, known/suspected causes, and subsequent remediation activities. All reports (e.g., EM reports) and documentation must be maintained in the pharmacy's records and available for Board inspection.

Please direct any questions to: **Pharmacy.Admin@mass.gov**